REMARKS

The specification has been amended to correct typographical errors in Table 2 and to more clearly set forth the information contained in that Table; no new matter has been added.

Claims 1-58 have been canceled without prejudice to present such claims in a subsequent application, and new claims 59-111 have been added. Support for the amendments to the claims and for the added claims is found in the claims as originally filed and throughout the specification, as for example at page 1, lines 33-35; at page 1, line 41 through page 3, line 6; at page 5, lines 3-8; at page 14, lines 27-31; at page 14, line 37 through page 15, line 3; at page 15, lines 26-40; at page 18, lines 31-33; at page 19, line 13 through page 20, line 34; at page 21, line 26 through page 22, line 8; and at page 31, lines 20-21; no new matter has been added.

Supplemental Information Disclosure Statement

Applicants thank the Examiner for bringing to their attention the lack of a translation of reference 1B (WO 01/66736), which was submitted in the March 2002 IDS. The Examiner is requested to note that a Supplemental Information Disclosure Statement with accompanying form PTO-1449 is being filed herewith, which contains a statement under 37 CFR 1.98(a) regarding WO 01/66736 and which correctly lists the translation information regarding that reference. Applicants have not had an English translation made of WO 01/66736. However, the Examiner is respectfully requested to note that reference 2B (EP 1 179 592 A1), which was previously submitted in the October 2002 Supplemental IDS, and the newly submitted reference 1A (US 2003/0008334 A1) are publications in the English language of the European and US applications, respectively, corresponding to the WO 01/66736 PCT publication. The EP 1 179 592 A and US 2003/0008334 A1 publications each appear to be a translation of the WO 01/66736 publication into English. The Examiner is respectfully requested to make the cited references 1A and 1B of record in the subject application.

Declaration of Inventors under 37 CFR § 1.131

Applicants submit herewith a Declaration by the inventors under 37 CFR 1.131 establishing a date of invention in the United States prior to April 1, 2000. The Declaration

has been signed by all of the inventors except one, Peter R. Baum, who is traveling overseas and is currently unavailable. A Declaration under 37 CFR 1.131, signed by all of the inventors, will be provided to the Examiner as soon as it is possible to do so.

Rejection under 35 U.S.C. §112, Second Paragraph

A. Claims 1, 2, and 4, and dependent claims 5-8, 10, 11, 19, and 54 were rejected under 35 U.S.C. §112, second paragraph, for allegedly being unclear due to the use of the following terminology in claims 1, 2, and 4 (emphasis added):

> A polypeptide *comprising* an amino acid sequence [having a certain structure], wherein a polypeptide *consisting of* said amino acid sequence [has a certain activity].

The Office Action contended that the use of both 'comprising' and 'consisting of' in the above type of claim was unclear. Applicants do not concede to the basis for the rejection; the above terminology is clear in that it indicates that the amino acid sequence of the claim is sufficient to provide a polypeptide consisting solely of said amino acid sequence with a specified activity. The claim as a whole may therefore be drawn to a polypeptide *comprising* such an amino acid sequence without creating any ambiguity. For this reason alone, the rejection of claims 1, 2, and 4 under 35 U.S.C. §112, second paragraph, may properly be withdrawn, and withdrawal of the rejection is respectfully requested.

Further, Applicants have canceled claims 1, 2, and 4, and none of the newly added claims use this terminology, obviating the basis for the rejection.

For at least the above reasons, withdrawal of the rejection of claims 1, 2, 4-8, 10, 11, 19, and 54 under 35 U.S.C. §112, second paragraph, is respectfully requested.

B. Claims 6 and 8 were rejected under 35 U.S.C. §112, second paragraph, on the basis that a recitation of "from *about* amino acid X to Y" made the claims unclear. Applicants do not accede to the basis for the rejection. Applicants have canceled claims 6 and 8 and none of the newly added claims use the phrase "from *about* amino acid X to Y", eliminating the basis for the rejection.

For at least the above reasons, withdrawal of the rejection of claims 6 and 8 under 35 U.S.C. §112, second paragraph, is respectfully requested.

Rejection under 35 U.S.C. §112, First Paragraph

Claims 1-10, 11, 19, and 54-58 were rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement.

The Office Action concedes at the top of page 3 that "the specification is enabling for a substantially purified polypeptide comprising an amino acid [sequence] of SEQ ID NO:2, 4, 6, 8, 10, 12 and 31, wherein SEQ ID NO:4, 6, 10, 12, and 31 compris[e] amino acids 74-152, wherein the polypeptide consist[s] of amino acid sequence that binds to nectin-1 for inhibiting endothelial cell migration." However, the Office Action expresses a concern that there is a lack of enablement for active variants with at least 80 or 90% identity to such amino acid sequences. For at least the following reasons, the concerns stated in the Office Action are misplaced, and the rejection of claims 1-10, 11, 19, and 54-58 under 35 U.S.C. §112, first paragraph, may properly be withdrawn.

I. Teaching of essential sequences.

One basis for the rejection of these claims is the misplaced assertion of the Office Action that the specification does not provide guidance as to which amino acid sequences are involved in inhibiting endothelial cell migration. First, as the examiner has conceded (see above), there is teaching in the specification of amino acid sequences that bind to nectin-1 for inhibiting endothelial cell migration. It is clear from Examples 4 through 6 of the specification (pages 53-56) that a soluble form of human nectin-3, including only the nectin-3 extracellular domain fused to an Fc polypeptide, is capable of binding to endothelial cells and inhibiting their migration. Further, the specification at page 4, lines 5-11 teaches the role of the extracellular domains of nectin polypeptides in binding activities, and in particular describes the three Ig domains of the extracellular domain, with the N-terminal Ig domain involved in binding to other nectins, and the third or C-terminal Ig domain involved in homodimerization. The specification at page 5, lines 5-8, also states: "Three extracellular Ig domains, common to members of the nectin polypeptide family, are located at about amino acids 74 through about 152, about amino acids 189 through about 250, and about amino acids 287 through about 342 for nectin-3α (SEQ ID NO:6), β (SEQ ID NO:12), and γ (SEQ ID NO:31)." Therefore, the specification provides teaching to those of skill in the art that the portion of the nectin-3 polypeptides involved in inhibition of endothelial cell migration includes the Ig domains of the extracellular region. For this reason, a purported lack of

teaching of regions related to biological function is not an adequate basis upon which to reject claims 1-10, 11, 19, and 54-58, which have been canceled, nor can this rationale be applied to the present claims, which all are drawn to polypeptides comprising at least a substantial portion of the nectin-3 extracellular domain.

II. Teaching of functional variants

The Office Action states at the bottom of page 4, "The skilled artisan would not reasonably expect a polypeptide having anything less than 100% identity over the full length of SEQ ID NO:2, 4, 6, 10, 12, or 31 to share the same function." However, this conclusory statement in the Office Action is inapposite for the following reasons. First, the specification clearly teaches that certain variants of the nectin-3 polypeptide sequences of SEQ ID NO:2, 4, 6, 10, 12, or 31 ***would*** be expected by those of skill in the art to be functional. At page 6, lines 22-33, the specification explicitly states [emphasis added]:

> Amino acid substitutions and other alterations (deletions, insertions, and the like) to the nectin amino acid sequences (*e.g.*, SEQ ID Nos:6, 12, or 24) are ***predicted to be more likely to alter or disrupt nectin polypeptide activities if they result in changes to the consensus residues of the amino acid sequences shown in Table 2, and particularly if those changes do not substitute an amino acid of similar structure*** (*e.g.*, such as substitution of any one of the aliphatic residues - Ala, Gly, Leu, Ile, or Val - for another aliphatic residue), or a residue present in other nectin polypeptides at that conserved position. ***Conversely, if a change is made to a nectin-3 (α, β, or γ) or nectin-4 polypeptide resulting in substitution of a residue at a position in the alignment that is not conserved from one of the other nectin and nectin-like sequences in Table 2, it is less likely that such an alteration will affect the function of the altered nectin-3 (α, β, or γ) or nectin-4 polypeptide***. For example, the consensus residue at position 98 in Table 2 is arginine, and some of the nectins have an lysine at that position. Accordingly, substitution of an lysine or the chemically similar histidine for arginine at that position are less likely to alter the function of the polypeptide than substitution of tryptophan or tyrosine.

This teaching of the specification provides clear guidance to those of skill in the art: making changes in residues at conserved positions in SEQ ID NO:2, 4, 6, 10, 12, or 31 (as shown in Table 2) creates more risk of alteration of the biological function of the polypeptide, whereas changes in nonconserved residues of Table 2 is less likely to alter biological function; and substitution of a residue that is chemically dissimilar to the conserved residue, or to the residue of another family member at that position in the alignment, is more likely to alter

biological function than substitution of a chemically similar residue. Any proposed variation in the amino acid sequence of SEQ ID NO:2, 4, 6, 10, 12, or 31 can be reviewed by those of skill in the art in light of the teaching of the specification, to determine the type of residues that would be affected by the variation (whether conserved in Table 2 or not), the nature of any substituted residues (whether chemically similar or not), and whether it is likely to be a functional variant. Therefore, the clear teaching and specific examples regarding functional variants that are provided by the specification show that there is no basis for the Office Action to support this rejection of claims 1-10, 11, 19, and 54-58.

Further, the references that the Office Action cites in support of this statement ("The skilled artisan would not reasonably expect a polypeptide having anything less than 100% identity over the full length of SEQ ID NO:2, 4, 6, 10, 12, or 31 to share the same function") are either inapposite, or are more supportive of the position that it ***is*** possible to make polypeptide variants that retain biological activity.

The Attwood and the Skolnik and Fetrow references, when viewed in their entirety, are primarily directed to the problems faced by annotators of sequence database entries when trying to make predictions of biological function based on sequence data *alone*. Therefore, they are not applicable to the disclosure of Applicants, in which functional data regarding the polypeptide sequences is presented (for example, Examples 4 through 6 at pages 53-56 of the specification). Further, the issues that the Attwood and the Skolnik and Fetrow references raise as being of concern to database annotators, are either not relevant to the nectin-3 polypeptides of the invention, or have been addressed by the disclosure of the specification. As one example, Attwood (2000, *Science* 290: 471-473) cautions against making a prediction of biological function on the basis of sequence similarity to only one of several functional modules or domains in a protein. This hypothetical concern is not applicable to the enablement of the claimed subject matter, because there is description in the specification of the *overall* similarity of the structure of nectin-3 polypeptides with other nectin polypeptides: the three Ig domains, the transmembrane domain, and the similarity of sequences at the intracellular C-terminus that are seen in the members of the nectin polypeptide family (for example, see pages 4-9 of the specification).

The Office Action cites Metzler *et al.* (1997, *Nature Struct Biol* 4: 527-531) in support of its conclusory statement that it is unpredictable if functional activity will be shared by two sequences having less than 100% sequence identity. In the third paragraph of page 4 of the Office Action, it is stated that Metzler *et al.* show that "*any* of a *variety* of single amino acid differences can alter or abolish the ability of CTLA4 to interact with its ligands ..."

(emphasis added). However, the Office Action fails to mention a critical fact about the amino acids that were mutated in the Metzler *et al.* reference: *all* of the mutations were made in residues that were highly conserved in CTLA4 family polypeptides (see Figure 2 of Metzler *et al.*), and would therefore be ***expected***, based on the teaching at page 6 of the specification as discussed above) to frequently result in changes in biological function. Because the results of Metzler *et al.* are based only on mutations at conserved positions, this reference cannot be cited for the proposition that *any* of a *variety* of single amino acid differences can alter or abolish biological activity. In fact, Metzler *et al.* provides experimental evidence in support of the teaching of the specification, namely that changes to conserved residues are likely to change the biological activity of a polypeptide.

The references cited in support of this basis for this rejection of claims 1-10, 11, 19, and 54-58 under 35 U.S.C. §112, first paragraph do not, despite the selective quotations offered in the Office Action, support the contention that the claims lack enablement. For this reason alone, the rejection of claims 1-10, 11, 19, and 54-58 under 35 U.S.C. §112 may properly be withdrawn.

III. Testable function

At the bottom of page 4 of the Office Action, it is stated that "The skilled artisan would not reasonably expect a polypeptide having anything less than 100% identity over the full length of SEQ ID NO:2, 4, 6, 10, 12, or 31 to share the same function" as the claim recitation "binds to nectin-1" was not considered to represent a 'testable function', because "even if the polypeptide binds to nectin-1, there are numerous functional activities encompassed besides binding to nectin-1". Even if this statement in the Office Action is assumed *arguendo* to be correct, it is unclear how this statement supports a rejection of the claims for lack of enablement, especially considering the apparently contradictory statement at the top of page 3 of the Office Action, "the specification is enabling for a substantially purified polypeptide comprising an amino acid [sequence] of SEQ ID NO:2, 4, 6, 8, 10, 12 and 31, ... wherein the polypeptide consist[s] of amino acid sequence that binds to nectin-1 for inhibiting endothelial cell migration." Applicants do not accede to this basis for the rejection, and respectfully submit that it has not been set forth clearly enough to be an adequate basis for the rejection of the claims. However, claims 1-10, 11, 19, and 54-58 have been canceled, and where the currently presented claims recite a testable function of nectin-3 polypeptides, that testable function is inhibition of endothelial cell migration. Therefore, this

basis for the rejection of claims 1-10, 11, 19, and 54-58 has not been adequately established, and in any case has now been rendered moot.

There were three points of argument that could be ascertained from the Office Action as supporting the rejection of claims 1-10, 11, 19, and 54-58 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement: the purported lack of teaching of essential sequences, functional variants, or a testable function. However, for at least the reasons presented above, Applicants have shown that the specification does indeed provide teaching of the essential sequences of the polypeptides; guidance for creating functional variants and avoiding non-functional ones; and a testable biological function. For at least these reasons, this rejection of claims 1-10, 11, 19, and 54-58 under 35 U.S.C. §112, first paragraph, has been overcome, and withdrawal of the rejection is respectfully request.

Rejection under 35 U.S.C. §112, First Paragraph

Claims 1-10, 11, 19, and 54-58 were rejected under 35 U.S.C. §112, first paragraph, for allegedly not being described in the specification. For at least the reasons presented below, this rejection has been overcome.

As the Office Action points out, these claims encompass both amino acid sequences specifically exemplified in the disclosure, and also variants of those polypeptides having biological activity. These claims each represent a genus of polypeptides related by both structure and function. However, in its rejection of these claims under the first paragraph of 35 U.S.C. § 112, the Office Action does not take into consideration all of the information presented in the specification, and known in the art, pertaining to nectin polypeptides such as the nectin-3 polypeptides of these claims.

Analysis of whether a claim meets the written description requirement involves consideration of the following types of information presented in the disclosure or known in the art (see the Synopsis of Application of Written Description Guidelines, page 8, at www.uspto.gov/web/menu/written.pdf):

A. Partial structure
B. Physical and/or chemical properties
C. Functional characteristics
D. Known or disclosed correlation between structure and function
E. Method of making
F. Combinations of A-E

These factors are to be weighed in view of the level of skill *and the knowledge in the art* and in light of and consistent with the written description.

The subject matter of the rejected claims 1-10, 11, 19, and 54-58 and the newly added claims is described by distinguishing identifying characteristics relating to categories A, C, and D above, and by F, a combination of these distinguishing identifying characteristics.

A) The members of the presently claimed genuses *share a distinguishing partial structure*: they comprise an amino acid sequence at least 80% identical to a portion of the nectin-3 extracellular domain comprising at least amino acids 74 through 152, 189 through 250, and 287 through 342 of SEQ ID NO:4, 6, 10, 12, or 31. This shared portion of the nectin-3 extracellular domain, representing the majority of the extracellular domain of mature nectin-3 polypeptides, in combination with the following additional distinguishing identifying characteristics, such as the known structure-function relationships described below, is sufficient to describe each claimed genus.

C) The members of the presently claimed genuses *share distinguishing functional characteristics*. As mentioned above, not only do the members of each claimed genus have substantial amino acid similarity to the majority of the nectin-3 extracellular domain, they also have the distinguishing functional characteristic of being able to inhibit endothelial cell migration, which can be demonstrated experimentally as shown in several Examples of the specification.

D) *There is a known correlation between structure and function for members of each genus.* Nectin polypeptides share a high degree of amino acid sequence similarity in the extracellular domain, as shown in Table 2 of the specification. The specification identifies the polypeptides of the invention as nectin polypeptides; ***those of skill in the art would apply the known structural and chemical properties of conserved residues within the extracellular domains, for example within the Ig domains, in the determination of the metes and bounds of the claimed genus of nectin-3 polypeptides***.

Those of skill in the art would therefore recognize that applicants had presented sufficient identifying characteristics to define each genus of structurally and functionally related nectin-3 polypeptides.

The Office Action cites *University of California v. Eli Lilly and Co.,* 43 USPQ2d 1398 (Fed. Cir. 1997), "*Lilly*", for the requirement that Applicants must demonstrate that they were in possession of the claimed invention. Some have mistakenly read the *Lilly* case as equating sufficient written description with explicit recitation in the specification. However, current Federal Circuit case law has made it clear that *Lilly* does *not* create a requirement for a particular form of disclosure, such as the amino acid sequences of polypeptide variants. In *Moba v. Diamond Automation*, No. 01-1063, -1083, slip op. (Fed. Cir. April 1, 2003), the Federal Circuit stated: "In *Enzo* and *Amgen*, the record showed that *the specification that taught one of skill in the art to make and use an invention also convinced that artisan that the inventor possessed the invention.* Similarly in this case, the *Lilly* disclosure rule does not require a particular form of disclosure because one of skill could determine from the specification that the inventor possessed the invention at the time of filing." (Citations omitted; emphasis added.) In the present specification, Applicants have provided detailed guidance on how to make variants of nectin-3 polypeptides that retain the biological activity of inhibiting endothelial cell migration and how to test such variants for this activity. Therefore, one of skill in the art would recognize that Applicants were in possession of variants of nectin-3 polypeptides that inhibit endothelial cell migration.

The specification provides sufficient identifying characteristics of the claimed subject matter, and provides sufficient teaching in how to make and use the polypeptides of the invention, to describe the subject matter of the claims and to demonstrate that Applicants possessed the claimed invention. For at least the above reasons, the rejection has been overcome, and withdrawal of this rejection of claims 1-10, 11, 19, and 54-58 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejection under 35 U.S.C. §102(a) on the basis of Reymond *et al.*

Claims 1-7, 10, 11, 19, and 54-58 were rejected under 35 U.S.C. §102(a) as anticipated by Reymond *et al.* (September 2000, *Gene* 255: 347-355). For at least the reasons below, this rejection has been overcome.

Applicants submit herewith a Declaration by the inventors under 37 CFR 1.131. The declarants describe the isolation of a DNA clone encoding a human nectin-3 polypeptide and the determination of the human nectin-3 amino acid sequence on a date prior to the September 2000 publication of the Reymond *et al.* reference. Accordingly, Applicants submit that they have established a completion of an embodiment of the invention in the United States prior to the date of the cited art.

In view of this Declaration, Applicants respectfully request withdrawal of the rejection of claims 1-7, 10, 11, 19, and 54-58 under 35 U.S.C. § 102(a).

Rejection under 35 U.S.C. §102(b) on the basis of Ottenwaelder *et al.*

Claims 1-6, 19, 54, and 57-58 were rejected under 35 U.S.C. §102(b) as anticipated by Ottenwaelder *et al.* (PIR database accession number T08732, 1999). For at least the reasons below, this rejection has been overcome.

The Ottenwaelder et al. publication discloses a partial sequence that has some amino acid sequence similarity to amino acids 143 through the C terminus of SEQ ID NO:6 of the present application. This partial amino acid sequence of Ottenwaelder et al. only has 10 amino acids of the N-terminal Ig domain (the N-terminal Ig domain being, for example, amino acids 74 through 152 of SEQ ID NO:6), and is therefore not likely to have nectin-1 binding activity or endothelial cell migration inhibitory activity (page 9, lines 7-9 of the specification). For this reason alone, the partial polypeptide disclosed in Ottenwaelder et al. cannot anticipate claims 1-6, 19, 54, and 57-58.

Furthermore, claims 1-6, 19, 54, and 57-58 have been canceled, and the newly added claims recite nectin-3 polypeptides, all of which comprise at least amino acids 74 through 152 of SEQ ID NO:6 or amino acid sequences substantially identical thereto. Therefore, the partial polypeptide disclosed in Ottenwaelder *et al.* does not anticipate the present claims.

For at least the above reasons, Applicants respectfully request withdrawal of the rejection of claims 1-6, 19, 54, and 57-58 under 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. §102(a) on the basis of Satoh-Horikawa *et al.*

Claims 1-7, 10, 11, 19, and 54-58 were rejected under 35 U.S.C. §102(a) as anticipated by Satoh-Horikawa *et al.* (April 2000, *J Biol Chem* 275: 10291-10299). For at least the reasons below, this rejection has been overcome.

Applicants submit herewith a Declaration by the inventors under 37 CFR 1.131. The declarants describe the isolation of a DNA clone encoding a human nectin-3 polypeptide and the determination of the human nectin-3 amino acid sequence on a date prior to the April 2000 publication of the Satoh-Horikawa *et al.* reference. Accordingly, Applicants submit that they have established a completion of an embodiment of the invention in the United States prior to the date of the cited art.

In view of this Declaration, Applicants respectfully request withdrawal of the rejection of claims 1-7, 10, 11, 19, and 54-58 under 35 U.S.C. § 102(a).

Rejection under 35 U.S.C. §103(a) on the basis of Reymond *et al.*, Ottenwaelder *et al.*, or Satoh-Horikawa *et al.* in view of U.S. Patent No. 6,472,520

and

Rejection under 35 U.S.C. §103(a) on the basis of Reymond *et al.*, Ottenwaelder *et al.*, or Satoh-Horikawa *et al.* in view of U.S. Patent No. 6,362,371

Claim 7 was rejected under 35 U.S.C. §103(a) as obvious in light of a combination of the Reymond *et al.*, Ottenwaelder *et al.*, or Satoh-Horikawa *et al.* references with U.S. Patent No. 6,472,520, and claim 8 was rejected under 35 U.S.C. §103(a) as obvious in light of a combination of the Reymond *et al.*, Ottenwaelder *et al.*, or Satoh-Horikawa *et al.* references with U.S. Patent No. 6,362,371. For at least the reasons presented below, these rejections have been overcome.

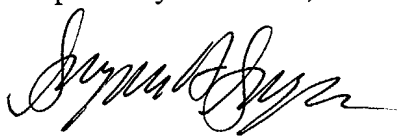
As described above, Applicants submit herewith a Declaration under 37 CFR 1.131 demonstrating completion of an embodiment of the invention in the United States on a date prior to the publication of either the Reymond *et al.* or the Satoh-Horikawa *et al.* references. Since Applicants' invention antedates the Reymond et al. and Satoh-Horikawa et al. references, the rejection of claims 7 and 8 under 35 U.S.C. §103(a) rests upon a combination of only the disclosure of Ottenwaelder *et al.* with U.S. Patent No. 6,472,520 or 6,362,371, respectively. The Ottenwaelder *et al.* publication teaches a partial 'hypothetical' protein that lacks almost all of the N-terminal Ig domain that is present in the human nectin-3

polypeptides of SEQ ID NOs 2, 4, 6, 8, 10, 12, and 31 of the present application, and is associated with nectin-1 binding and endothelial cell migration inhibitory activity (page 9, lines 7-9 of the specification). Therefore, even in combination with U.S. Patent No. 6,472,520 or 6,362,371, the Ottenwaelder *et al.* publication neither teaches nor suggests a nectin-3 polypeptide having nectin-1 binding and/or endothelial cell migration inhibitory activity, and the rejection of claims 7 and 8 under 35 U.S.C. §103(a) cannot be maintained on the basis of a combination of these references. Further, as the Ottenwaelder *et al.* publication does not teach a function for the disclosed polypeptide, there would be no motivation to apply the teaching of U.S. Patent No. 6,472,520 or 6,362,371 to the Ottenwaelder *et al.* polypeptide, as there is no suggestion that such a combination would be desirable. Therefore, a prima facie argument for obviousness of the claims cannot be made on the combination of the Ottenwaelder *et al.* reference with U.S. Patent No. 6,472,520 or 6,362,371.

For at least these reasons, the rejections of claims 7 and 8 under 35 U.S.C. §103(a) have been overcome, and withdrawal of the rejections is respectfully requested.

If a telephone interview would be helpful in advancing the prosecution of this application, Applicants' attorney invites the Examiner to contact her at the number provided below.

Respectfully submitted,



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